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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,782	10/17/2003	Harald W. Sontheimer	051530-5004-02	7705

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EXAMINER	
CHEN, SHIN LIN	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/686,782	SONTHEIMER ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 15-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 15-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10-17-03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of group I, claims 1-6, in the reply filed on 2-22-06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 7-14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 2-22-06.

Examiner thanks applicants for pointing out that claims 2-14 have been canceled in the preliminary amendment filed 10-17-03. Applicants' preliminary amendment filed 10-17-03 and amendment filed 2-22-06 has been entered. Claim 1 has been amended. Claims 15-28 have been added. Claims 1 and 15-28 are pending and under consideration.

Double Patenting

3. Applicant is advised that should claim 22 be found allowable, claim 28 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

4. Applicant is advised that should claim 1 be found allowable, claims 26 and 27 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing,

despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

5. Applicant is advised that should claim 20 be found allowable, claim 21 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Specification

6. The disclosure is objected to because of the following informalities: The phrase "US Provisional Application 60/009,293" on page 1 line 4 in the amendment to the specification filed 10-17-03 is incorrect. The correct application number is 60/009,283.

Appropriate correction is required.

7. The amendment filed 10-17-03 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the amendment to the specification by inserting on page 1 "The present application is a divisional application of Application 09/296,031 ... **all of which are herein incorporated by reference in their entirety**". The oath/ declaration only claims priorities of 08/774,154 and 60/009,283 but fails to incorporate herein by reference. Thus, the amendment filed 10-17-03 introduces new matter into the specification.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1 and 15-25 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: Where the pharmaceutical composition is administered to, how the pharmaceutical composition is administered, and whether the neuroectodermal tumor has been treated or whether the symptom of the neuroectodermal tumor is ameliorated by the treatment. The method step fails to refer back to the preamble of the claimed method.

10. Claims 26-28 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: Where the pharmaceutical composition is administered to, how the pharmaceutical composition is administered, and whether the neuroectodermal tumor has been treated or whether the symptom of the neuroectodermal tumor is ameliorated by the treatment. The method step fails to refer back to the preamble of the claimed method.

Claim Rejections - 35 USC § 112

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1 and 15-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1 and 15-28 are directed to a method of treating an individual having a neuroectodermal tumor comprising administering a pharmaceutical composition comprising chlorotoxin fused to a cytotoxic moiety and a pharmaceutically acceptable carrier. Claims 15 and 21 specify the cytotoxic moiety is selected from the group as recited in the claims. Claims 16 and 20 specify the tumor is selected from the group as recited in the claims. Claim 17 specifies the chlorotoxin can be native, synthetic, or recombinant chlorotoxin. Claims 18 and 19 specify the neuroectodermal tumor is a glioma. Claims 23 and 24 specify the composition is suitable for parenteral administration, such as intravenous, intramuscular, intrathecal and subcutaneous administration.

The specification only discloses the detection of glioblastoma, neuroblastoma, medulloblastoma, pheochromocytoma and metastatic melanoma etc. in a tissue sample by using chlorotoxin. The claims encompass treating various neuroectodermal tumors by administering a pharmaceutical composition comprising a chlorotoxin fused to any cytotoxic moiety or cytotoxic moiety recited in claim 15, i.e. gelonin, ricin, saponin, pseudomonas exotoxin, pokeweed antiviral protein, diphtheria toxin, or any complement protein, via various administration routes so as to provide therapeutic effect for treating said neuroectodermal tumor in vivo. The specification fails to provide adequate guidance and evidence for how to treat a neuroectodermal tumor, such as ependymomas, medulloblastoma, pheochromocytoma, glioblastoma,

neuroblastoma, or any metastatic tumors of neuroectodermal origin in the brain, by using a pharmaceutical composition comprising a chlorotoxin fused to a cytotoxic moiety, such as gelonin, ricin, saponin, pseudomonas exotoxin, pokeweed antiviral protein, diphtheria toxin, or any complement protein, via various administration routes in vivo.

The claims read on protein therapy in vivo. Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101) states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy (e.g. bridging pages 81-82). Gorecki, 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198), reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy (e.g. abstract). Similarly, the administration route, the location of the target cells, the stability of the polypeptide, and the amount of the polypeptide that reaches the target site will determine the efficiency of protein transfer and whether said protein can provide therapeutic effect for a particular disease in vivo. The state of the art of protein therapy was unpredictable at the time of the invention. There are various barriers before a protein can reach its target cells, for example, layers of dermal cells, blood vessel wall cell membranes, proteases and lysosomal degradation within cells, extracellular matrix between cells, and gastrointestinal digestive acids,

and as discussed below, there is blood-brain barrier for treating brain tumors. Whether sufficient chlorotoxin-cytotoxic protein moiety would reach target neuroectodermal tumor in a subject to provide therapeutic effect depends on the concentration of the chlorotoxin complex used, the administration route, the location of the target cells and the stability of the polypeptide etc.

Further, several neuroectodermal tumors are located in the brain. It was well known in the art that brain is separated from general circulation by the blood brain barrier. Castro et al., 2001 (Histl. Histopathol., Vol. 16, p. 1225-1238) points out that the brain offers a particular challenge for gene delivery to its constituent cells because it is "made up of mostly non-dividing cells, the skull limits direct injection of vectors into the brain, the blood brain barrier inhibits the easy entry of vectors injected into the bloodstream, and post mitotic target cells restrict what type of vector can be used to deliver genes to the brain" (e.g. abstract). "The main challenges holding back the widespread clinical implementation of neurological gene therapy are technical limitations of current transgene delivery system, i.e. the gene transfer vectors...short term expression of the potentially therapeutic transgenes, coupled to the instability of vectors in the presence of the inflammatory and immune responses directed against the vectors and/or transgenes, reduce the efficiency of delivered therapeutic transgenes...Factors affecting vector stability in target cells/tissues, remain to be identified" (e.g. page 1226, right column). Similarly, there is the brain-barrier to the delivery of a protein, such as the chlorotoxin fused to a cytotoxic protein moiety as recited in the claims, to the brain. It is unclear how the chlorotoxin complex would reach the targeted tumor in the brain via oral administration, intravenous administration, intramuscular administration, subcutaneous administration, or intrathecal administration etc., to a subject. The specification fails to provide adequate guidance and evidence for whether sufficient

chlorotoxin fused to any cytotoxic moiety could reach target neuroectodermal tumor in a subject via various administration routes such that therapeutic effect can be obtained for treating said neuroectodermal tumor in vivo.

In addition, the amino acid sequence of a protein determines its structural and functional properties, and predictability of which amino acids can be removed from a protein's sequence and still result in similar activity is extremely complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's structure from mere sequence data are limited. Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) teaches that "A single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding" (e.g. Title). Davis, C. G., 1990 (The New Biologist, Vol. 2, No. 5, p. 410-419) reports that EGF repeats appears in an extraordinarily diverse group of molecules, including growth factors, transmembrane molecules, extracellular matrix proteins, and soluble secreted proteins, and it is often difficult to deduce what contribution the EGF repeat makes in a totally unrelated protein (e.g. p. 410, left column). It appears that EGF repeat can contribute to different biological functions in different amino acid contexts, i.e. different proteins. Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may

not tell you something about its function" (e.g. p. 36, box 2). The claims encompass various different cytotoxic moiety and the recited different toxins, antiviral protein, and complement proteins. Different proteins have different amino acid sequences and the biological function of a protein was unpredictable from mere amino acid sequence at the time of the invention. The dose of the cytotoxic moiety, the stability of said cytotoxic moiety during protein transfer in vivo, and the effect of the cytotoxic moiety on treating neuroectodermal tumor all vary among different cytotoxic moieties., however, the specification fails to provide such specific guidance for those various cytotoxic moieties recited in the claim. Thus, one skilled in the art would not know how to treat numerous neuroectodermal tumors in vivo by using various chlorotoxin-cytotoxic moiety complexes via various administration routes so as to provide therapeutic effect for treating said neuroectodermal tumor.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the working examples given and scarcity of guidance in the specification, the level of skilled artisan which is high, and the unpredictable nature of the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Shin-Lin Chen, Ph.D.

SHIN-LIN CHEN
PRIMARY EXAMINER